IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1648
ZEBEDEE et al.	Examining Attorney: Zachariah Lucas
Serial No.: 10/677956	
Filed: October 1, 2003	Date: January 7, 2007 Pasadena, California
For: METHODS AND SYSTEMS FOR PRODUCING RECOMBINANT VIRAL ANTIGENS	

DECLARATION UNDER 37 CFR 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Torsten B. Helting, declare:

1. That I was the President of Pharmacia Genetic Engineering Inc. ("Phage") La Jolla, CA an original co-assignee of the subject application. The other original co-assignee was the New York Blood Center ("NYBC"). Phage and NYBC were parties to a collaborative research and license agreement to investigate recombinant HCV proteins for the detection of HCV antibody.

2. That Phage has been dissolved and its assets assumed by Pharmacia Biosystems, which subsequently changed its name to Pharmacia Biotech, Inc. Pharmacia Biotech Inc. was subsequently merged into Pharmacia & Upjohn Company which thereafter assigned its rights to Amersham Pharmacia AB, which by an Agreement dated August 19, 1998, assigned to Torsten Helting its right and interest in the subject application. By the same Agreement with Amersham Pharmacia AB, dated August 19, 1998, the above-mentioned collaborative research agreement was also assigned to myself (Torsten B. Helting). I have subsequently assigned my interest in said patent application to Bioprocess Pty Ltd, the current assignee of record in the United States Patent and Trademark Office, of which I am the Managing Director (and sole Director).

3. I am making this Declaration as the beneficial owner of this patent application in lieu of the named inventors since I possess the relevant records, have personal knowledge, and the inventors have scattered and in the case of Dr. Prince, retired. It would be difficult and time consuming to contact and brief them within the time period set by the United States Patent and Trademark Office for filing a response to the Office Action and maintain the "Special" status.

4. All of the acts and events described in this Declaration occurred in the United States.

5. Upon close-down of operations at Phage relevant documents were taken into storage in San Diego and later transferred to Pharmacia, Inc., Piscataway, New Jersey for further storage in accordance with corporate storage policies. I did keep certain records including copies of laboratory notebooks and other laboratory records as a precautionary measure to be able to offer assistance in cases where I anticipated that my assistance would be required within the framework of a consultancy agreement with Pharmacia for several years following termination of Phage. I was permitted to purchase my office computer from Pharmacia which contained my own correspondence which was electronically stored as Word Perfect files. These files are still available and were copied to 5 1/4 diskettes when the computer became obsolete and had to be replaced. I am still in possession of these diskettes including three diskettes containing my correspondence from 1990. This correspondence was, and still is, organized according to a time line with a separate directory for each year, a subdirectory for each month of that year, and that said monthly subdirectory contains separate files for each day of said month, each day-file containing the letters written on said day. The exhibits presented herein and referencing my correspondence are true printouts from the original 5 1/4 diskettes in my possession.

6. The collaborative effort with the research group of Dr. Alfred M. Prince at the NYBC, directed towards obtaining useful clones derived from the Non A- Non-B hepatitis virus was a consequence of the agreement signed on March 30, 1990. Prior to the agreement itself, Phage had entered into a secrecy agreement with NYBC on

January 8, 1990, thus enabling a more open exchange pertaining to a joint effort, which was discussed, in person, with Dr. Prince during his visit to Pharmacia Genetic Engineering Inc. on February 23, 1990. A memorandum of the meeting (Exhibit 1) was prepared on February 24, 1990, and the computer file is still available. As item 3) of the memorandum, it is explicitly stated that:

> The availability of gene libraries and clones derived from these libraries at the Blood Center on the one hand, and the molecular biology expertise on the other, constitutes an excellent fit for a rapid joint effort directed primarily towards expressed gene products for diagnostic use. (underline added).

The rationale for such an effort was based on the realization that the newly introduced antigen for HCV diagnostics (commonly referred to as "C-100", while helpful in the determination of the immune status of chronic Hepatitis C virus disease, was less useful in detecting the presence of HCV antibody in recently infected individuals. This had become apparent by studies published during 1989 and early 1990 (see, e.g., Weiner et al., Lancet, vol. 335 pp. 1-3) using the C-100 antigen in immunoassays to determine the immune status vis-à-vis said antigen. DNA clones spanning approximately 7000 bases of the Hepatitis C agent had been isolated and their sequence determined, and by comparison to other viral agents the Hepatitis C agent had been classified to belong to the general class of Flavi or Pesti viruses. By

inference, the sequence information at hand suggested that the identified clones encoded nucleic acids relating to the non-structural elements of this family of viruses. However, there was, at the time, no such information available relating to HCV structural antigens (i.e., a putative capsid and or envelope component). We reasoned that once the complete sequence information had become available, such similar structures might be found to be encoded within the Non-A, Non-B viral genome as well. To explore the possibility of obtaining newly cloned and hitherto unknown regions of the Non-A, Non-B agent and determine their potential for improved diagnostic applications and possibly vaccine development, we considered it to be highly desirable to pool our resources which were complementary. NYBC had years of experience with blood borne diseases in general, and extensive research in conjunction with the Non-A, Non-B Hepatitis agent in particular (Hutch viral strain related materials), and Phage, having developed powerful capability and proven expertise in genetic engineering and gene expression technologies. Fortuitously, pertinent sequence information relating to these putative structural components of the virus became available shortly after commencement of the joint collaboration effort between Phage and NYBC.

7. That during my tenure as President of Phage, I was actively involved in directing and monitoring staff in a variety of research projects, including the execution of the collaborative research project with the original co-assignee, NYBC, leading to the subject application. At that time, the inventors Suzanne Zebedee and Mark S. Nasoff worked under my supervision at Phage. During the collaborative research project

beginning in early 1990 and continuing through June to November 1990, I conferred with the inventors, including Dr. Genevieve Inchauspe and Dr. Prince who worked at NYBC, and, pursuant to the agreement between Phage and NYBC, also reported their work to me on a frequent and regular basis.

8. The availability of DNA sequence information pertaining to the Non-A, Non-B capsid region in June, 1990, precipitated an immediate effort to obtain useful clones from this portion of the genome using the above-mentioned source materials available to us.

9. That, based on computer files and authentic records including laboratory protocols , I have established the chronology of the findings leading up to the filing of two patent applications during the second half of 1990, i.e., United States Patent Application Serial Nos. 07/573,643, filed on August 27, 1990 and 07/616,369 filed on November 21, 1990 as follows:

a) Conception and Diligence

The first capsid polypeptide (CAP-N, aa., 1-74 of the capsid sequence) was obtained by first performing a PCR reaction using target nucleic acids derived from HCV infected chimps and primer oligonucleotides 690 and 694, which were ordered (in addition to simultaneously ordered oligonucleotides 691 and 693, respectively, also

designed for PCR experiments pertaining to the HCV capsid region) from the oligonucleotide synthesis unit of Phage on June 20 and 21, 1990 by Dr. Zebedee, as evidenced by Exhibits 2 and 3 which are copies of documents prepared by Dr. Zebedee. Per date-stamped protocol showing the absorption spectra of the purified oligonucleotides, these became available for further experimentation on June 27, 1990 and were immediately subjected to a series of PCR reactions (Exhibit 4, which is Dr. Zebedee's laboratory notebook 51, p.64, ff). Subsequent identification/isolation procedures of several PCR-based gene products via agarose and polyacrylamide electrophoresis, said procedures based on predicted vs. actual size of the PCR products, lead to the subcloning of many isolated PCR products.

Anticipating obtaining new and useful clones within the near term, a memo was sent to our patent attorney and dated July 6 to prepare for a patent application (Exhibit 5). At this time, no useful Hepatitis C clones from the capsid region had been isolated, however, several subclones of PCR derived inserts had been obtained and were subjected to DNA sequence analysis to unequivocally identify the material(s) derived from the HCV capsid region by virtue of sequence homology with capsid related DNA isolates. On July 17, 1990 (Exhibit 4, which is the laboratory notebook of Suzanne Zebedee) a clone assigned the identifier No 690694-92u with the definitive, relevant capsid sequence was selected as starting material for expressing the CAP-N polypeptide (the sequence analysis was repeated and confirmed as being 1 to 74 on July 19, 1990, Exhibit 4, Dr. Zebedee, Notebook 51, p. 78). The effort to insert the

isolated DNA into a suitable form for expression was initiated on July 17 by Dr. Nasoff (Exhibit 6, notebook 63, p. 4).

A few days later, Dr. Nasoff had clear evidence of substantial gene expression, based on clone 690694-9u, of the capsid protein (aa 1-74, CAP-N). Per faxed letter (Exhibit 7) dated July 23, 1990, I asked Dr. Prince to send us a panel of seroconversion specimens to test the performance of the 1-74 capsid antigen by Western blot to establish the binding affinity between the Cap N antigen and a panel of sera containing HCV antibody taken at spaced intervals following infection to demonstrate the utility in earlier detection of HCV antibody. It was anticipated that a seroconversion panel with several specimens obtained at timed intervals post infection and characterized with regard to detection of antibody to C-100 was the most straightforward way to demonstrate the hypothesis that the capsid antigen might prove more useful than the state of the art antigen in detecting presence of anti-HCV antibody earlier than heretofore.

b) Reduction To Practice

On the same day, July 23, 1990, Dr. Prince, assignor to NYBC, ordered sera containing HCV antibody to be pulled from his inventory of Chimp seroconversion panels (Exhibit 8, computer file Dr. Prince C:\WP\EXPERIMENT\HCV.PCR, copy of printout available, said printout entitled, "SERA TO BE PULLED FOR PCR TESTING

AND FOR WESTERN BLOT STUDIES AT PHAGE") The protein synthesis of CAP-N in induced bacteria using the pGEX-3X-CAP-N vector was demonstrated by Dr. Nasoff on July 25, 1990 (Exhibit 6 Notebook 63, p 18). Five Members of the above-mentioned Serumpanel just made available by Dr. Prince (i.e., the CHIMP59 seroconversion panel) with samples from weeks 8-20 post-infection, were used for the Western blot experiment in the course of applying the following experimental steps: Growth and induction of E. coli cells transformed with the expression vector; Breakage of the bacterial cells after induction and separation of the components via polyacrylamide electrophoresis; Transblotting the separated polypeptides of the bacterial lysate on to a membrane of nitrocellulose; Incubating individual strips of the nitrocellulose blot with a dilution of several members of the seroconversion panel; Washing the serum-incubated strips to remove unbound materials, followed by labeling any bound antibody with a radiolabeled antibody to the bound antibody; Washing the strips again to remove unbound radiolabel, and then developing a radioimage of any radioactive band present on the strips; and, Examining the image. The film was developed and ready for visual inspection on Saturday, July 28, however, the series of steps which precede the actual demonstration of the presence of an early emerging, demonstrable anti-capsid antibody had been initiated prior to July 26 and thus merely confirm the results anticipated in the course of designing this experiment. Rather than using a known high titer serum specimen to demonstrate that the expressed Cap-N antigen was recognized by the antibody, the experiment was designed to immediately compare the performance of said antigen with the known performance of the state of the art antigen C-100 (Exhibit 6,

Notebook 63, p. 20, and printout by Dr. Prince, Exhibit 8 on the CHIMP59 seroconversion panel). The Western blot test (Exhibit 9) is an immunoassay, and the results as shown by the radioimage of July 28, 1990 showed the effectiveness of the Cap N antigen 1 to 74 in that HCV antibody is clearly detected with the serum sample obtained at week 12, two weeks earlier than with the state of the art assay (Exhibit 8).

I, Torsten B. Helting, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued therefrom.

Date: January 7, 2007

Respectfully submitted,

Torsten B. Helting


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